THE SPECIFIC RADIOSENSITIVENESS OF LYMPHOCYTES—ITS SIGNIFICANCE IN RADIOTHERAPY*

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THE specific radiosensitiveness of different varieties of cells has been so thoroughly tested and proved by innumerable experiments on animals that it deserves to be recognized as a law. And yet, if we may judge by present-day writings, the existence of such a law and of the experimental grounds on which it firmly rests is not so well known as one would expect it to be. Opinions are given daily, and so-called scientific contributions are prepared which ignore the fact as well as its medical implications. This is no doubt due to failure to keep abreast of the large number of experiments in this field of medicine and to the tendency of many writers to adopt too readily and to reproduce the plausible but unsound views of others without critical analysis. As an example of this tendency I should like to submit the case of the lymphocyte, which, of all the cells in the body, is by far the most sensitive to irradiation. The fact itself is well known, but its therapeutic implications are not commonly realized. Nowhere in the field of radiotherapy can a more instructive example of the specific sensitiveness of cells be found.

THE LYMPHOCYTES AND IRRADIATION

For many years a multitude of inflammatory disorders have been subjected to roentgen and radium rays with more or less effect, but the mechanism of the action of the rays is still a subject for debate, probably because many radiologists are not so familiar as they might be with the experimental background of radiotherapy. Heineke (1903-1905) was one of the first to make a breach in the veil of obscurity which, until that time, had surrounded the action of irradiation on living cells. The most important result of his experiments on a large number of white mice, rats, guinea pigs, rabbits, and dogs was to bring to light the exceptional sensitiveness of lymphocytes to roentgen rays and radium. He found that, when the entire body of animals of different species was exposed to large doses of one or the other form of radiant energy, the animals invariably died after an interval which varied according to the dose of rays and the size and age of the animals. But regardless of the ability of the animals to tolerate irradiation, he observed at necropsy that, although most of the organs were free from perceptible abnormality, the spleen, mesenteric nodes and other lymph nodes, and intestinal lymph follicles showed marked destruction of lymphocytes, and the degree of cellular disintegration varied according to the dose of rays and the interval between irradiation and microscopic examination. As the number of intact lymphocytes diminished the stroma became more and more prominent. The lymphocytic degeneration in the spleen and lymph nodes was often so great that most of the malpighian corpuscles or lymphoid follicles disappeared as such and could be recognized only by the blood vessels and by the concentric arrangement of the stroma of these structures. The destruction of lymphocytes was found to begin about two hours after irradiation and to be characterized by disorganization and fragmentation of the nuclear chromatin of the cells, scattering of the fragments of chromatin between the remaining intact cells and in the spaces of the reticular stroma, where the fragments gathered into clumps or balls. The result was almost complete destruction of the lymphoid tissue in about twenty-four hours, and this was accompanied and followed by progressive reduction in volume or atrophy of the affected structures. Then the clumps or balls of degenerate chromatin were gradually taken up by some of the reticular cells, which thus assumed a phagocytic property and swelled as the amount of ingested chromatin débris increased. The same changes were observed in the spleen, mesenteric lymph nodes, solitary follicles of the intestine, in the lymphoid tissue of the vermiform appendix, and even in the bone marrow. The pathologic changes were greatest in the germinal center of the lymphoid follicles, whence they extended toward the periphery.

The phagocytic disposal of the degenerate nuclear chromatin continued until the lymphocytes in the follicles were largely destroyed, but a small percentage of these cells appeared to resist the action of the rays. After a number of hours the phagocytic reticular cells themselves began to disappear; the chromatin débris ingested by the phagocytes appeared to undergo intracellular digestion, because the number and size of the ingested fragments diminished steadily. All that remained after the phagocytes had disappeared was the connective tissue framework, the blood vessels, and a number of round cells with a bright nucleus. Soon after the beginning of lymphocytic disintegration, cells three or four times larger than lymphocytes, with a large, eosinophilic body of protoplasm and a large, oval or round, vesicle-shaped nucleus appeared in the germinal center. As the destruction of lymphocytes progressed these epithelioid cells formed large clumps, gradually assumed a concentric arrangement and formed structures suggesting epithelial pearls. This process continued for several days, when the concentric, epithelioid structures diminished in size, and the appearance of the cells gradually approximated that of ordinary connective tissue cells, and finally disappeared. Two or three days after exposure to roentgen rays, degenerative alteration of other cells, notably the polymorphonuclear leukocytes and eosinophils, also became perceptible, and many of these cells disappeared

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from the splenic pulp and bone marrow. The degree of lymphocytic destruction appeared proportional to the length of exposure to the rays, and Heineke attributed the difference in degree of the tissue changes noted to variation in the focal-skin distance and in the thickness of the intervening tissues. In other animals irradiated for varying periods and examined from ten days to three weeks later, more or less regeneration of the lymphoid tissue was observed.

The action of irradiation on the lymphocytes and on lymphoid tissues in general has been fully confirmed by many subsequent experimenters, among whom may be mentioned Warthin (1906), Krause and Ziegler (1906-1907), Fromme (1917), Hall and Whipple (1919), Hartman (1920), Warren and Whipple (1922), Jolly (1924), Tsuzuki (1926), and Piepenborn (1929). Similar effects were obtained with radium by London (1903), Heineke (1904), London (1905), Thies (1905), and Lazarus-Barlow (1922). Warthin's description of the effect of roentgen rays on the lymphoid structures corroborates the observations of Heineke, except that, by examining the tissues soon after irradiation, Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and the cellular degeneration continued for several days. Rudberg, Aubertin and Bordet, Arella, Regaud and Crémieu, and many others, have likewise shown that roentgen and radium rays exert precisely the same influence on the small round cells of the thymus gland, and their work strongly supports Hammar's conclusion that the small cells of the thymus gland are indeed lymphocytes. Others, notably Senn (1903), Heineke (1903, 1905), Guilloz and Spillmann (1904), Aubertin and Beaujard (1904, 1905, 1908), Brown (1904), Bryant and Crane (1904), Capps and Smith (1904), Helber and Linser (1905), Russ (1919, 1921), Leitch (1921), Aubertin and Delamarre (1908), Benjamin, von Reuss, Sluka and Schwartz (1906), and Taylor, Witherbee and Murphy (1919), have proved that the lymphocytes in the circulating blood are equally sensitive to irradiation and that they also are destroyed in large numbers by exposure to roentgen or radium rays.

APPLICATION OF FACTS TO CLINICAL RADIOTHERAPY

How may these facts be applied to clinical radiotherapy, and how closely does clinical radiotherapy correspond to the experimental data? It has long been known that many acute and chronic, suppurative or nonsuppurative, inflammatory conditions are readily amenable to irradiation, and in some of these conditions roentgen-ray or radium treatment has been found to be the therapeutic method of choice. As examples, I might mention furuncle, carbuncle, delayed resolution in pneumonia, trachoma, erysipelas, and parotitis. Many other pathologic lesions of inflammatory character might be added to the list, but those mentioned are sufficient to bring out the relation between the effect of irradiation on such lesions and the specific sensitiveness of lymphocytes.

FURUNCLE AND CARBUNCLE

Coyle (1906), Dunham (1916), Carp (1928), and others, have established the fact that acute inflammation of this kind, especially when treated during the stage of maximal leukocytic infiltration, which is to say before the stage of frank suppuration, often responds remarkably well to irradiation. In many cases the pain disappears within a few hours, and the redness and swelling subside rapidly after suitable exposure to irradiation. Coyle reported three cases of carbuncle in which exposure to roentgen rays was followed almost immediately by relief from pain and in which the lesion healed in a few days without suppuration. Dunham (1916), at the suggestion of Wainwright, treated sixty-seven carbuncles, giving a full therapeutic dose of rays generated at a potential equivalent to a spark-gap of nine inches, filtered through three millimeters of aluminium, at a focal-skin distance of eight inches, for thirty-five milliampere minutes (more than ten Kienböck units). Pain sometimes increased during the first twelve hours, but ceased within forty-eight hours. The lesions then softened as the result of suppuration and drainage through a small incision, or suppuration did not occur. The results were so satisfactory that Dunham was moved to state that "nothing in all radiotherapy gives such positive and uniformly perfect results as the treatment of a carbuncle." Carp (1927) successfully treated with roentgen rays twelve patients suffering from nondiabetic carbuncle. Nine other patients apparently had to be operated on, and one patient died. Inasmuch as several methods of treatment had been used in many cases, Carp was not certain to which method the result should be credited. He concluded that radical operation is preferable in large carbuncles, whether the patient is diabetic or nondiabetic, but that in other carbuncles treatment by roentgen ray yields good results. The treatment is not uniformly successful, however, and this is probably due to factors within the lesions; these will be considered later. Treatment during the suppurative stage is less successful and its effect usually is less striking, but even then it is often of distinct value.

PNEUMONIA

Musser and Edsall (1905), impressed by the remarkable metabolic changes they had found in patients with leukemia treated with roentgen rays, suggested the possible advantage of such treatment for unresolved pneumonia. They reported one case in which irradiation was followed by rapid resolution and improvement, but stressed the point that such an effect could not be expected after organization had occurred. Edsall and Pemberton (1906), described three additional cases of delayed pneumonic resolution, in which moderate irradiation of the lungs promptly initi-

ated resolution, with correspondingly striking subsidence of the clinical manifestations. They held that the treatment could not be effective after organization of the pneumonic exudate, and they considered active, continued inflammation, with fever and toxemia, and tuberculosis as contraindications. At that time ferments occupied an excessively prominent place in biologic and medical thought, and Edsall and Pemberton expressed the idea that the rays act on the pneumonic process by accelerating the action of ferments and stimulating autolysis, but they admitted the "widespread and excited tendency to give ferments a more important place than is their due." For some reason the influence of roentgen rays on delayed resolution in pneumonia, revealed by such well-known clinicians, remained unutilized for ten years, when Quimby and Quimby (1916) confirmed the experience of Musser, Edsall, and Pemberton in twelve cases, four of which were described in detail. Although resolution had been delayed for some time, it progressed rapidly after roentgen irradiation of the lungs, and the patients promptly recovered. So gratifying were the results that Quimby and Quimby were prompted to state that "no pathologic process in the body responds quicker to an x-ray exposure than the nonresolution following pneumonia," and they attributed this effect to destruction of leukocytes infiltrating the lungs. Krost (1925) supplemented the foregoing reports by adding twelve other cases, in ten of which a single exposure of the thorax to roentgen rays of rather long wavelength for five minutes led to improvement in the symptoms and rapid recovery. Krost expressed the belief that irradiation stimulated phagocytosis. Additional evidence of the resolving action of roentgen rays on pneumonic exudates was furnished by Torrey (1927) and others.

Heidenhain (1927) claimed that small doses of roentgen rays also had a favorable influence on postoperative pneumonia and recorded forty-eight cases, in more than 80 per cent of which the course of the disease was said to have been shortened. He obtained equally favorable results in more than half of twenty-four cases of pneumonia unrelated to surgical intervention. Other favorable testimony was furnished by Heidenhain and Fried (1924), Kaess (1925), Fried (1926), Holzknecht (1926), Gadjanski (1927), Glas (1927), Fried (1928), Holst (1929), Merritt and McPeak (1930), and others. Hell (1929) was not so successful. Success attended treatment in only three of twenty-four cases, but the data furnished are insufficient to explain failure in the other cases.

As has been mentioned, Musser and Edsall, and Edsall and Pemberton thought the action of roentgen rays on delayed resolution was to stimulate autolysis by increasing the activity of the ferments. Quimby and Quimby ascribed the influence of irradiation on resolution to destruction of the infiltrating leukocytes. Krost held that the rays stimulated phagocytosis. These various interpretations appear more divergent than they really are. Although proof is lacking, it seems probable that the activation in ferment action and autolysis invoked by Musser, Edsall, and Pemberton, the destruction of infiltrating leukocytes mentioned by Quimby and Quimby, and by Pordo, and the increase in phagocytosis referred to by Krost, represent only different phases of the same effect. Experimental evidence of the great susceptibility of the leukocytes, especially the lymphocytes, to irradiation has been presented. The destruction of large numbers of such cells soon after moderate irradiation and the phagocytosis of the nuclear débris of the destroyed cells has been described. This undoubtedly explains the increase in phagocytosis and autolysis, and the failure of irradiation after the onset of organization.

TRACHOMA

Mayou (1902) called attention to the value of radiotherapy in trachoma by reporting the instance of a girl, aged fourteen years, with bilateral trachoma and thick, fleshy pannus in both eyes; the left eye was completely cured after twenty-two three-minute exposures to soft roentgen rays. The right eye, treated with a solution of copper sulphate, improved much less in the same time, but eight exposures to roentgen rays completed the cure of this eye also. Mayou (1903) recorded the cases of fifteen other patients treated with roentgen rays; nine were influenced favorably, and five of these were permanently cured. The others had recurrences or were still under treatment. Mayou thought the effect on the lesions was due to leukocytosis induced by the rays. Stephenson and Walsh (1903) also described two cases of trachoma cured by roentgen-ray treatment. Additional evidence of the potency of irradiation in trachoma was furnished by Bettremieux (1903), Cassidy and Rayne (1903), Geyser (1903-1904), Goldzieher (1904), Pordo (1904), Newcomet and Krall (1904), Vasyutinski (1904), Horniker and Romanin (1905), Stargardt (1905), Thielemann (1905), Kassabian (1906), Coleman (1907), Stargardt (1912), Jacqueau, Lemoine, and Arcelin (1920), Rollet and Bussy (1920), Cochard (1921), Meldolesi and Sabbadini (1923), Meldolesi (1924), Lane (1924), Sabbadini (1926), and others. In some of the cases in which the condition was reported as cured the trachomatous manifestations recurred, but many other patients remained free from disease, either permanently or for a long time. Cochard (1921) was able to cure two patients permanently and to bring about marked improvement of six others, but some of these had recurrences later. Resumption of treatment, however, was again followed by rapid decrease and disappearance of the granules, and this led Cochard to the probably sound conclusion that the initial treatment had not been sufficiently thorough or had not been continued long enough. In only two of the eleven cases included in his thesis did the treatment fail to benefit the patient, and in these the disease had been of long standing and was associated with advanced sclerosis.

Harman (1905) apparently was the only observer to report failure to influence trachoma by roentgen rays. It is permissible to surmise, therefore, that his technique may have been faulty. Terrien (1919) stated that irradiation caused the lymphoid hyperplasia to retrogress and the granulations to disappear, but that recurrence was the rule. Derby (1924) also wrote disparagingly of the value of roentgen-ray treatment in trachoma; his opinion was not based on personal experience, but on a cursory and incomplete review of the literature. It is impossible to read the communications of Thielemann (1905), Cochard (1921), and Sabbadini (1926), to mention only these three, without being convinced that roentgen rays have a real and substantial effect on the lesions of trachoma. This effect appears to be greatest in the early stages of the granular form of the disease; irradiation has little, if any, effect when the inflammation has been present a long time and the lymphoid granulations have been replaced by connective tissue sclerosis.

Beck (1905), Cohn (1905), Falta (1905), Horniker and Romanin (1905), and Zelenkowski (1906) testified that radium also caused the lesions of trachoma to retrogress rapidly, but many of these early records were not explicit with reference to permanency of cure or duration of improvement. Birch-Hirschfeld (1905) also reported improvement in ten cases, but in nine the disease recurred. Esdra (1906), Fortunati and Esdra (1908), and Flemming (1913) noted cure or improvement in some cases, but in the majority of cases it was impossible to be certain that radium was responsible for the slight amelioration in the condition of the patients. Although the foregoing reports do not furnish sufficient information for analysis, the impression is derived that failure to obtain more substantial results may have been due to inadequate treatment or faulty technique. This impression is strengthened by a review of the communications of Zelenkowski (1906), Jacoby (1906), Kardo-Sisoyeff (1906), Dinger (1906), Neuschuler and Steiner (1906), Thibault (1906), Norton (1907), Zelenkowski (1908), Muller and Högler (1922), Sallmann (1923), Wassing (1923), Lane (1924), and others.

All the foregoing reports, except that of Harman, concur in showing that exposure to roentgen or radium rays causes the trachomatous granules to diminish rapidly in size and number and to disappear, and this is accompanied by early relief from pain and improvement in the other symptoms. Zelenkowski appears to have been the first to ascribe this influence of irradiation on the lesions of trachoma to the destructive action of the rays on the lymphocytes which are such an important element of the granulations, but it remained for Sabbadini (1926), whose communications are probably the best on the subject, to prove that irradiation causes the lymphoid elements and granulomatous papillae to disappear and to be replaced by young connective tissue, and the epithelium to regenerate.

ERYSIPELAS

During the last few years it has been found that this disease, also, when it does not complicate conditions such as diabetes or nephritis, often responds well to radiotherapy. This is especially true in adult patients when the treatment is given early. For some reason children, on the whole, do not receive so much benefit. On adults and on some children, however, the effect of moderate irradiation is to cause the fever to abate in from twelve to twenty-four or thirty-six hours and the disease to stop spreading and to recede gradually. In some cases, after a variable period of improvement or complete disappearance of clinical manifestations, the disease may recur, and renewal of treatment in such cases may prove less effective than in the first instances. By moderate irradiation is meant exposure of the affected area or region to from one-third to two-thirds of an erythema dose of roentgen rays of medium wavelength, generated at a potential equivalent to a sphere-gap tension of from 120 to 140 kilovolts, and filtered through four millimeters of aluminium. An apparently important point is that the treatment should not be limited to the visible part of the lesions, but should extend into the adjacent normal tissues well beyond the perceptible limits of the involved territory.

The mechanism by which the rays exert their beneficial influence in this disease has not yet been clearly established, but the significance of lymphocytes in the defense of the organism against infection and the known sensitiveness of these cells to irradiation make it appear likely that, in this condition, as in so many other inflammatory processes, the rays act by destroying lymphocytes infiltrating the lesion or circulating in the blood vessels which supply the affected area. In favor of this view is the rapidity with which the symptoms often abate and the physical signs disappear after exposure to a small or moderate dose of roentgen rays. This in itself points to destruction of lymphocytes as at least the primary and direct result of irradiation, because the lymphocytes are the only cells in the body, except the basal epithelium of the salivary glands, which react to irradiation at a rate which even approaches this rate. The indirect consequences of such destruction and their therapeutic implications will be considered. Also variation in the degree of leukocytic infiltration in different cases may explain the partial or complete failure of irradiation in some cases.

PAROTITIS

Acute parotitis has long been a sinister complication of certain surgical operations. Its incidence is low in general operations, but is high in operations on the large intestine. Rankin and Palmer have found that the disease is from fifteen to twenty times more common after surgical interventions on the colon than after all other operations; it occurred after approximately one of 150 operations on the large bowel. The mortality, as reported by various observers, ranged

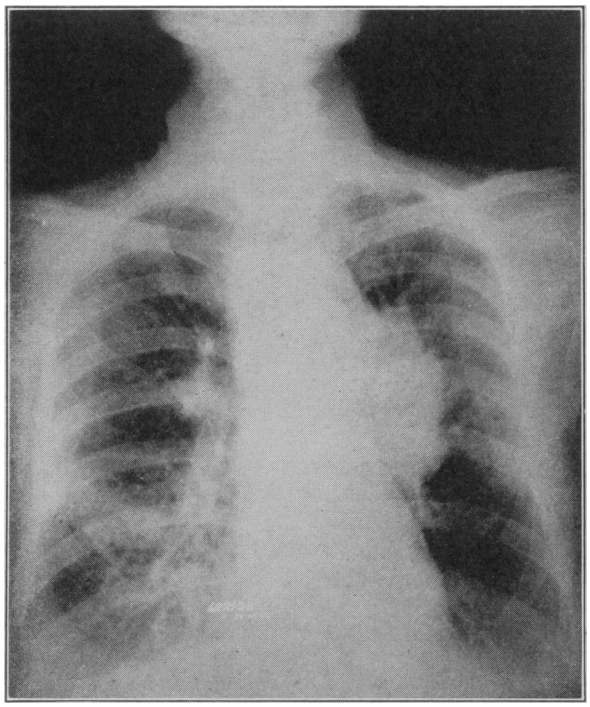

Fig. 1.—Large mediastinal tumor before treatment.

between 35 and 60 per cent, and according to Rankin and Palmer depends on the primary condition, the extent and severity of the operation, and on suppuration of one or both parotid glands. When they tested the therapeutic effect of moderate doses of radium applied soon after the onset of the parotitis (infiltrative stage) they found that the inflammatory process abated in most cases within from twenty-four to forty-eight hours, that suppuration was prevented, and that the mortality was correspondingly reduced. After treatment by radium, suppuration was only one-tenth as frequent as after ordinary methods of treatment as reported by others. These conclusions were based on twenty cases, in only two of which surgical drainage had to be instituted.

During the last two years a few such cases have also been treated with roentgen rays, with equally encouraging results. This seems to furnish another example of the property of radiation to influence favorably many varieties of inflammation. An interesting feature of the reaction of acute parotitis to irradiation is that the effect is much the same and becomes perceptible at about the same time after exposure as other acute inflammatory processes. There is reason to believe, therefore, that the mechanism involved is essentially the same.

MODE OF ACTION OF IRRADIATION

The natural tendency would be to think that the effect of the rays on acute inflammatory lesions may be due to a bactericidal action on the infecting organisms, but the almost constantly negative results of the large number of experiments undertaken to test the influence of irradiation on many kinds of bacteria renders such an explanation untenable. The experiments on animals previously described have shown that leukocytes, especially the lymphocytes in the spleen; in the mesenteric and other lymph nodes, in the intestinal lymph follicles, and even in the lymphoid tissue of the vermiform appendix and lungs, are exceptionally sensitive to roentgen or radium rays, and that a large number of such cells in the irradiated territory may be caused to disintegrate. The chief points to bear in mind are that the destructive action of the rays begins soon after exposure, although visible effects may not become perceptible for several days, and that a considerable degree of lymphocytic disintegration occurs even after a small dose of irradiation.

One of the earliest and most important steps in the natural defense of the organism against most infectious processes is leukocytic, and especially lymphocytic, infiltration around the site of infection. Therefore, when an inflammatory lesion is irradiated, destruction of the infiltrating lymphocytes is to be expected. But since leukocytic infiltration is such an important factor in the defense against infection, the question naturally arises of why the destruction of a large number of the lymphocytes infiltrating such lesions may not do more harm than good naturally arises. The only answer is that no one has yet submitted any evidence of such ill effect. Always the influence of irradiation has been favorable or the rays have failed to alter the course of the inflammatory process. When I first attempted to ascertain the therapeutic value of irradiation for lesions of this character this question was uppermost in my mind, and I carefully analyzed all the known

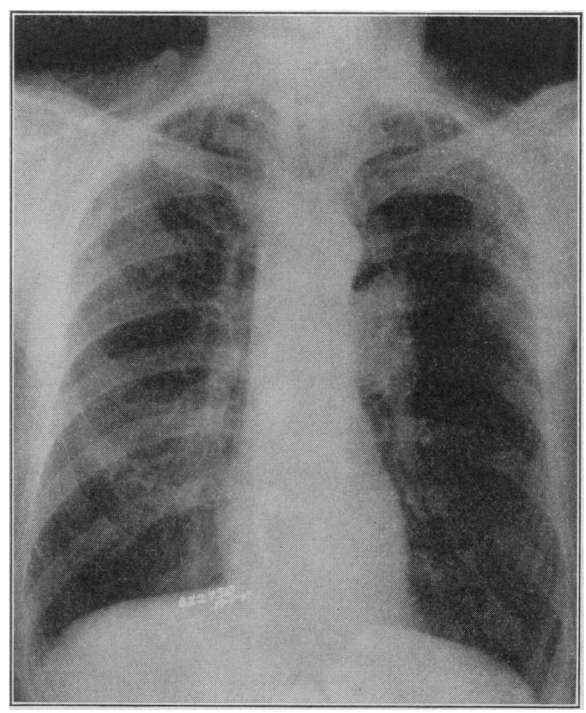

Fig. 2.—Patient represented in Figure 1 twenty-one days later and two weeks after a course of roentgen irradiation. Marked retrogression of the mediastinal tumor is shown.

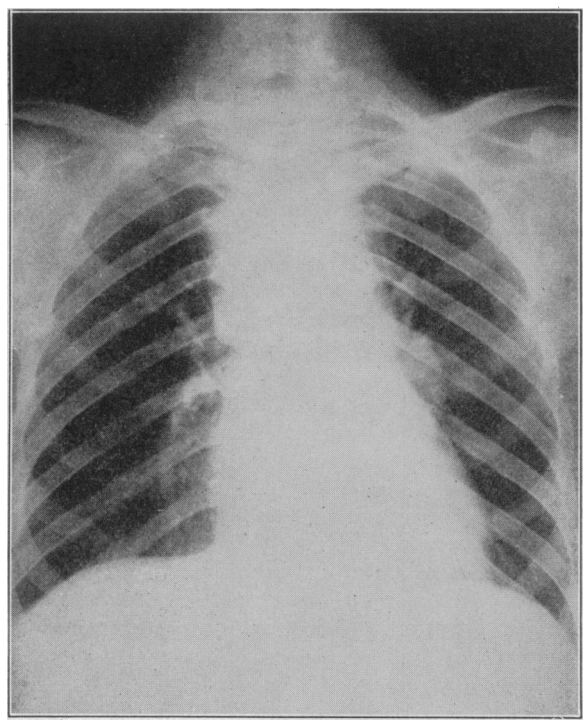

Fig. 3.—Large mediastinal tumor before treatment.

experimental and clinical facts. The first patients were treated with great caution. Now, after treating a large number of patients over a period of several years, I can testify that if, in some cases, radiotherapy remains without favorable effect, it has never had an unfavorable action. Moreover, in the majority of cases in which benefit has been derived it has been found that a small or moderate dose of rays of medium quality is sufficient to produce the desired results. Large doses of rays of short wavelength are not required and are indeed undesirable, probably because a smaller proportion of such rays is absorbed by the tissues at the level of the lesion.

How may such an apparent paradox be explained? After trying to correlate the experimental and clinical observations, I have formulated the following hypothesis which appears to harmonize with all the known facts. If it can be assumed that the leukocytes, and especially the lymphocytes, which the organism mobilizes around the site of infection represent an effort to localize the infection and to get rid of the infectious material by phagocytosis or otherwise, it must also be assumed that the infiltrating cells contain or elaborate within themselves the protective substances or other means which enable them to destroy or neutralize the bacterial or other toxic products which give rise to the defensive inflammation. If these assumptions are well founded, it seems not unreasonable to deduce that irradiation, by destroying the infiltrating lymphocytes, causes the protective substances contained by such cells to be liberated and to be made even more readily available for defensive purposes than they were in the intact cells. There can be little question that the rays act by destroying the infiltrating leukocytes, and that the value of radiotherapy depends chiefly on such action. In favor of this view are the points already mentioned, namely, that the rapidity of recession of irradiated inflammatory lesions corresponds closely to the rate at which the normal lymphocytes are known to be influenced by exposure to the rays, and that a small or moderate dose of irradiation is sufficient or even preferable to a large dose. Other circumstances pointing in the same direction are that radiotherapy is most beneficial during the infiltrative stage and less beneficial during the suppurative stage (although some benefit may be derived) of the inflammatory process, and that, although many such lesions respond rapidly to treatment of this kind, some respond less rapidly or do not respond at all. In connection with the last point, variation in the degree of leukocytic infiltration of different lesions of the same character or of similar lesions of different character is a well-known pathologic fact. Therefore, it is at least permissible to believe, or even to expect, that the degree of leukocytic infiltration must influence the action of the rays, because the rays can destroy lymphocytes only in proportion to the number of such cells. This is undoubtedly related to and probably explains the fact that, although many inflammatory lesions are influenced favorably by irradiation, some react much less or fail to show any reaction.

LYMPHOID TUMORS

The significance of the specific sensitiveness of lymphocytes is as important in tumors arising in lymphoid organs and structures as in purely

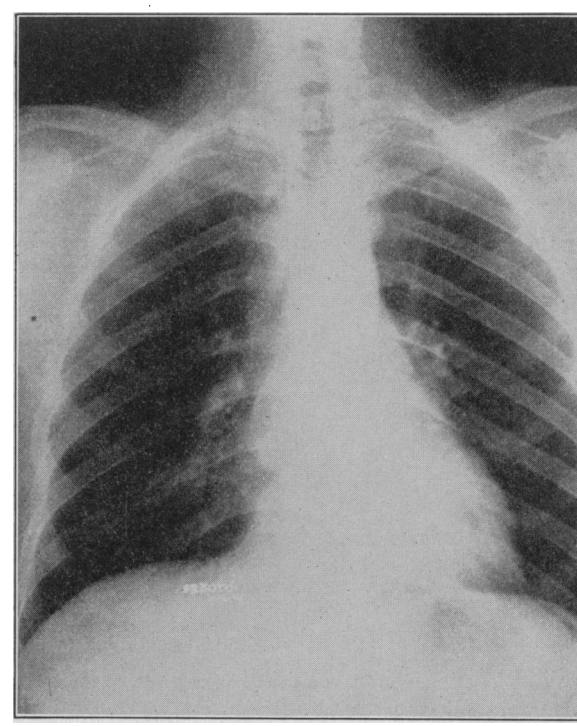

Fig. 4.—Patient represented in Figure 3 one month later and three weeks after a course of roentgen irradiation. Marked reduction in the size of the mediastinal tumor is shown.

inflammatory lesions. The unrestrained lymphocytic hyperplasia of lymph nodes which constitutes the chief characteristic of Hodgkin's disease, lymphosarcoma, and lymphatic leukemia, and of the spleen in myelogenous leukemia, provides the best example. The power of irradiation to cause such adenopathy to retrogress or actually to disappear for short or long periods has made radiotherapy the most satisfactory means of temporarily controlling the malignant tendency of such conditions. Here also it is found that the rate of regression of the adenopathy is precisely the rate at which normal lymphocytes are known to be destroyed by irradiation. This significant fact enables the experienced radiologist not only to improve the condition of the patient and relieve many distressing symptoms, but actually to distinguish the group of diseases or tumors collectively known as lymphoblastoma from all other tumors or conditions with which they might be confounded. The radiotherapeutic test is of distinct value whenever biopsy cannot be done or does not furnish conclusive information. In some cases, indeed, the radiotherapeutic test is more reliable than microscopic examination of sections of tissue. A diagnosis by the reaction of the hyperplastic lymphoid structures can almost always be made in from a few days to two or three weeks. The volume of the enlarged lymph nodes or spleen rapidly diminishes, and the clinical manifestations of pressure on other organs, blood vessels, or nerves, promptly abate. Pain of weeks' or months' standing is often relieved in two or three days. The very rapidity of action indicates that the disease condition is one affecting lymphoid structures. Figure 1 shows a large mediastinal tumor before treatment, and Figure 2 shows the mediastinum of the same patient three weeks after a single course of roentgen irradiation. Such rapid regression of a tumor in such a short time is characteristic of lymphoid tissue and corresponds with the rate of destruction of normal lymphocytes by irradiation. This is true regardless of the region involved. A carcinoma of the bronchus, esophagus, or lung never undergoes so great a change in such a relatively brief space of time; indeed, few intrathoracic carcinomas or sarcomas ever retrogress to such an extent, regardless of time. The different forms of lymphoblastoma, it is true, vary somewhat in radiosensitiveness, and a measure of variation also occurs among lymphoblastomas of the same kind, but such variation is almost never great enough to cause confusion. Figures 3 and 4 represent another example. The former shows a mediastinal tumor before treatment, and the latter the same mediastinum three weeks after a single course of roentgen irradiation. Such a degree of radiosensitiveness is so typical of lymphoid tissues and tumors in general that it constitutes a valuable therapeutic test and can render great service in the differential diagnosis of certain varieties of tumor. This is especially important when tissue cannot be removed for microscopic examination or when the patient refuses to submit to such a procedure. Indeed, when the clinical manifestations are not clearly defined or when, as in some cases of lymphoblastoma, a mediastinal or other tumor is not accompanied by palpable enlargement of the superficial lymph nodes, the reaction of the growth to irradiation may generally be depended on to make a sharp distinction between lymphoid growths and neoplasms of other derivation. Long experience has established the great reliability of such a radiotherapeutic test, which is being used daily to identify lymphoid tumors, as well as to exclude such processes.*

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* The complete list of 104 references will be found in the reprints.

UNEXPLAINED EOSINOPHILIA*

REPORT OF CASES

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DISCUSSION *by Ernest H. Falconer, M. D., San Francisco; and Charles L. Connor, M. D., San Francisco.*

EOSINOPHILIA, a frequent clinical finding, is ascribed to many different causes. Physiological eosinophilia,[2] so-called, occurs after prolonged fasts, and after hemorrhage, or loss of hemoglobin in hemoglobinuria. In convalescence [1] from the acute evanthemata, eosinophilia is frequently observed. The average eosinophil count of individuals residing in tropical or subtropical climates is said to be nearer ten than the commonly accepted standard of three. Eosinophils seem to bear a relation to the functions of the glands of sex, as these cells are moderately increased after coitus and female castration, and during lactation, menopause, and the puerperium.

DRUGS WHICH INDUCE AN EOSINOPHILIA

Many different drugs induce an eosinophilia, and such an increase is observed after the administration of arsenic, nuclein, pilocarpin,[3] camphor, dinitrobenzol, acetanilid, sodium solicylate, mercury, potassium iodid, and pituitary extract.[5] Eosinophilia has been observed after poisoning with phosphorus and with carbon dioxid.[4]

The increase in eosinophils following infestation with animal parasites [6] is well known. Parasites evoking such a response are the Oxyuris, Ascaris, Echinococcus, Trichina, Uncinaria, Taeniae saginata and solium, Dibothriocephalus, Bilharzia and Filaria bancrofti. Infestation with the Leishmania, Trypanosome or Ameba may or may not be accompanied by eosinophilia.

THEORY OF PHAGOCYTIC FUNCTION

Some authorities, notably Fiessinger and Mesnil, believe that eosinophils have an important phagocytic function, and protect the body particularly against toxins. Evidence favoring this theory is the eosinophilia observed in infants following the ingestion of a protein to which they are unaccustomed,[7] and in adults the eosinophilia

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